



# Xylitol treats nasal mucosa in rhinitis medicamentosa: an experimental rat model study

Behram Cam<sup>1</sup> · Murat Sari<sup>2</sup> · Ahmet Midi<sup>3</sup>  · Ozgül Gergin<sup>4</sup>

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## Abstract

**Objective** Rhinitis medicamentosa is drug-induced rhinitis which occurs by prolonged and overdose usage of topical nasal decongestants. There is not much of treatment choice rather than nasal steroids. In this pathological study, we have been aimed to represent the healing effects of xylitol on damaged nasal mucosa due to rhinitis medicamentosa.

**Method** 30 Wistar rats were separated into 5 groups. During 2 months, oxymetazoline was given to the first group, and saline was given to second group intranasally. First and second group animals were examined at the end of 2 months and rhinitis medicamentosa was detected. Oxymetazoline was given to the third, fourth, and fifth groups during 2 months. Then xylitol solution, mometasone, and saline were applied, respectively, for 15 days. After the experiment, rats' nasal mucosas were evaluated histopathologically.

**Results** Xylitol and mometasone were found to be more effective than the control group in terms of histopathological changes. Effectivity of xylitol and mometasone was compared and not a significant value was determined.

**Conclusions** According to the results, xylitol solution is effective as mometasone, usable and well-priced in the treatment of rhinitis medicamentosa. More comprehensive and ultrastructural studies on animals and human studies with rhinometric evaluation should be performed.

**Keywords** Rhinitis medicamentosa · Xylitol · Mometasone · Nasal mucosa · Nasal decongestants

## Introduction

Rhinitis medicamentosa is a nasal inflammation caused by prolonged and overdose usage of topical nasal decongestants. However, it may occur by many other drugs such as antihypertensives, oral contraceptives, and 5-phosphodiesterase inhibitors. The definition of the disease is made as prolonged and overdose usage of topical nasal decongestants, especially the oxymetazoline and xylometazoline [1, 2]. The cases have become addictive to nasal decongestants to cope with nasal obstruction, but this causes a paradox which patients could not heal. Rhinitis medicamentosa causes various histopathological changes in nasal mucosa, and atrophic rhinitis may be seen in severe cases [3]. Nasal obstruction is a major manifestation of the disorder. The other rhinitis symptoms are less prominent. The exact incidence of the disease is not known but it is known how frequent these medications are used [3, 4]. Histopathologic studies show that not only congestion and

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✉ Ahmet Midi  
ahmetmidi@yahoo.com

Behram Cam  
behramcam@yahoo.com

Murat Sari  
drmuratsari@yahoo.com

Ozgül Gergin  
gerginogul@yahoo.com

<sup>1</sup> Department of Ear Nose Throat, Acibadem Healthcare Group, Acibadem Kocaeli Hospital, Izmit, Kocaeli, Turkey

<sup>2</sup> Department of Ear Nose Throat, Marmara University, Ministry of Health, Pendik Education and Research Hospital, Istanbul, Turkey

<sup>3</sup> Department of Pathology, Istanbul Bahcesehir University, Faculty of Medicine, Sahrayı cedit mah, Batman sok, no 66, Göztepe, Kadıköy, Istanbul, Turkey

<sup>4</sup> Department of Ear Nose Throat, Ministry of Health, Ümraniye Education and Research Hospital, Istanbul, Turkey

edema occurred in nasal mucosa [5]. Nonetheless, mucosal changes, epithelial destruction, cilia loss, chronic inflammation, and fibrosis can be seen in the disease process [6]. In the medical therapy of the disease generally nasal steroids and saline, irrigations are used [3, 7]. In this study, a new drug—xylitol is used in the treatment of rhinitis medicamentosa. It is hypothesized that xylitol may have a mucosa healing effect on the nasal mucosa. Xylitol is a five-carbon sugar structure used in the food industry as a sweetener [8]. It became popular after found to be effective to decrease the incidence of dental caries [9]. Due to its antimicrobial properties, also otorhinologic studies have been carried out [10–12]. The molecular properties of xylitol are hydrophilicity and osmoregulatory effectiveness [13]. In this study, we aimed to show whether there is any therapeutic effect of xylitol on histopathological changes in rhinitis medicamentosa.

## Materials and methods

The study was carried out at M. University Medical Faculty, Experimental Animal Research and Application Center after the approval of M. University Experimental Animal Ethics Committee dated 14.10.2010 and numbered 73.2010.mar.

Thirty healthy 6-month-old Wistar albino rats, those weighted approximately 250–300 g, were used. In a period of a week, all animals were inspected and no pathology was detected. Experimental animals were housed in steel cages and fed with standard laboratory food. No feed and fluid restrictions were made.

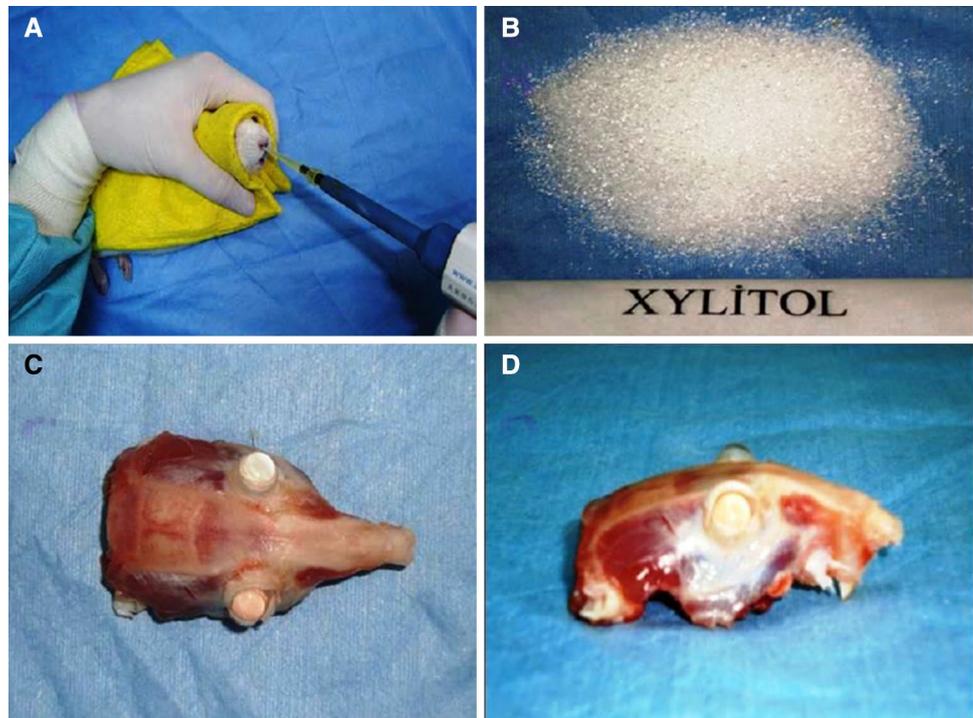
Animals were divided into five groups of six animals in each group (Table 1).

Drugs were applied intranasally using a micropipette (Fig. 1a). In group 1, 50  $\mu$ l of 0.025% oxymetazoline (Iliadin, Merck, Germany) was applied to each nostril three times a day for 2 months. In group 2, as control of group 1, 50  $\mu$ l saline was applied in the same manner. In the groups 3, 4, and 5, oxymetazoline was applied as in group 1 for 2 months, and then the third group received 5% xylitol solution for 15 days, the fourth group received mometasone furoate (Nazoster, Santa Farma, Turkey) which was applied for 15 days, and finally, in the fifth group, as a treatment control group, saline was applied for the last 15 days. Xylitol solution was prepared to form crystallized xylitol (Hyllen Co Ltd. China) dissolved in physiologic saline (Fig. 1b).

**Table 1** Experimental groups

1. Group	Oxymetazoline for 60 days
2. Group	Saline for 60 days
3. Group	Oxymetazoline for 60 days, followed by xylitol for 15 days
4. Group	Oxymetazoline for 60 days, followed by mometasone for 15 days
5. Group	Oxymetazoline for 60 days, followed by 15 days saline

**Fig. 1** **a** Intranasal drug administration to the rat, **b** pure crystalline xylitol, **c**, **d** specimen images after decapitation



All rats were anesthetized with intraperitoneal ketamine (Ketalar, Eczacıbaşı, Turkey) and xylazine (Rompun, Bayer, Turkey). Perfusion–fixation procedure was performed with 10% formaldehyde. Rats were decapitated while mandibles are resected and skin was removed (Fig. 1c, d). Specimens were placed in 10% formaldehyde and sent to pathology. Samples were randomly numbered for the blind evaluation of the pathologist.

Samples were fixed with 10% buffered formaldehyde for 3 days, and decalcification was performed using 10% EDTA 2Na (pH 7.4). After 3 h, running water was used to wash away the decalcification solution, and the tissue was fixed for two more days in formaldehyde.

Specimens were sliced coronally from anterior to posterior with 2 mm thickness. An automated tissue tracking device was used for routine processing. After performing the procedure, tissue slices were embedded in paraffin and sectioned 4 µm thickness in the coronal axis. Sections were stained with hematoxylin and eosin, and evaluated using light microscopy (Olympus CX31RTSF Olympus Optical, Japan) by a pathologist blinded to the treatment groups. Evaluation of the parameters was performed in areas with the most changes. Scoring was performed similarly to the previous studies [14–17].

The parameters and evaluation criteria were determined as follows:

Congestion, edema, cilia loss, epithelial damage, chronic inflammatory cell infiltration, fibrosis, and increase of fibroblasts parameters are evaluated in four

degrees: none, mild, moderate, and severe. Epithelial thickness is measured by numbers of the cells in epithelium as one, two, three, and four and over. Mucosal thickness is measured by an oculometer and categorized into 4°: below 200 µm, between 200 µm and 250 µm, between 250 µm and 300 µm, over 300 µm.

SPSS 15.0 was used for analyses and a biostatistician reviewed the results. Differences in the related parameters in all groups were calculated using Chi-square ( $\chi^2$ ) test.

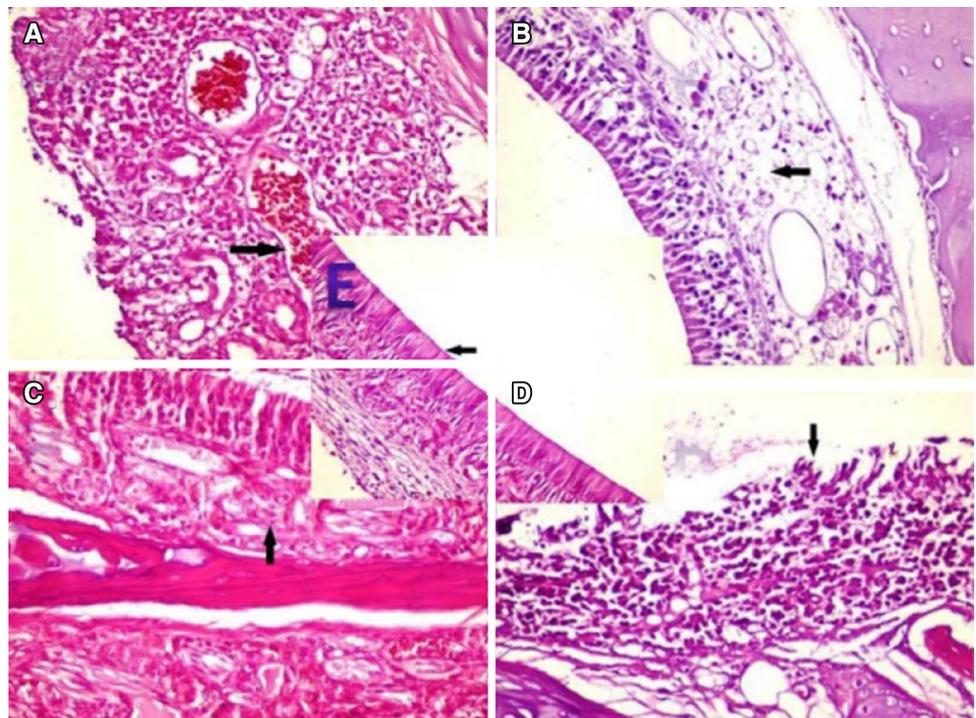
## Results

Evaluation of the histopathological parameters of congestion, edema, cilia loss, epithelial damage, chronic inflammatory cell infiltration, fibrosis, and increase of fibroblasts were done separately below and the results are given in Table 2.

### Congestion

It can be briefly defined as an increase in vascularization and vascular diameter in nasal mucosa and concha parenchyma. In groups 3 and 4 were showed statistically significant and equal recovery. No significant value was obtained between groups 3 and 5, and between 4 and 5, but there was a numeric difference that groups 3 and 4 had better results (Fig. 2a) (Table 2).

**Fig. 2** **a** Congestion in group 1. Enlarged vessels filled with erythrocytes (H&E  $\times$  400). **b** Edema, congestion, and cilia loss in group 5. Enlarged vessels in the subepithelial area surrounded by edema. Cilia structures are absent on surface epithelium. (H&E  $\times$  400). **c** In the xylitol group (group 3), no edema under the epithelium is observed (H&E  $\times$  400). **d** In the treatment control group (group 5), diffuse cilia loss, intense chronic inflammation cells on the floor. Epithelial cells in large areas on the surface are not observed, the arrow shows residual epithelium (H&E  $\times$  400). **e** Minimal chronic inflammatory cell infiltration in the mometasone group (4th group) under the epithelium (H&E  $\times$  400)



**Table 2** Histopathological findings

Distribution of histopathological findings according to groups	1. Group		2. Group		3. Group		4. Group		5. Group		P
	n	%	n	%	n	%	n	%	n	%	
Cilia loss	-	-	6	100	5	83.3	5	83.3	-	-	1&2: 0.007, 1&3: 0.029, 1&4: 0.025, 2&5: 0.002, 3&5: 0.007, 4&5: 0.011
None	-	-	6	100	5	83.3	5	83.3	-	-	
Mild	3	50.0	-	-	1	16.7	-	-	-	-	
Moderate	2	33.3	-	-	-	-	1	16.7	3	50.0	
Severe	1	16.7	-	-	-	-	-	-	3	50.0	
Congestion	n	%	n	%	n	%	n	%	n	%	1&2: 0.002, 1&3: 0.002, 1&4: 0.002, 1&5: 0.050, 2&5: 0.046
None	-	-	4	66.7	3	50.0	3	50	-	-	
Mild	-	-	2	33.3	3	50.0	3	50	2	33.3	
Moderate	-	-	-	-	-	-	-	-	2	33.3	
Severe	6	100	-	-	-	-	-	-	2	33.3	
Edema	n	%	n	%	n	%	n	%	n	%	1&2: 0.029, 1&3: 0.029, 2&5: 0.011, 3&5: 0.011, 4&5: 0.050
None	-	-	5	83.3	5	83.3	3	50	-	-	
Mild	3	50	1	16.7	1	16.7	3	50	3	50	
Moderate	2	33.3	-	-	-	-	-	-	3	50	
Severe	1	16.7	-	-	-	-	-	-	-	-	
Squamous metaplasia											
None	2	33.3	6	100	5	83.3	5	83.3	-	-	1&2: 0.050, 2&5: 0.002, 3&5: 0.013, 4&5: 0.013
Mild	2	33.3	-	-	1	16.7	1	16.7	5	83.3	
Moderate	2	33.3	-	-	-	-	-	-	1	16.7	
Severe	-	-	-	-	-	-	-	-	-	-	
Chronic inflammatory cell infiltration											
None	-	-	-	-	2	33.3	4	66.7	-	-	1&2: 0.002, 1&3: 0.007, 1&4: 0.025, 2&5: 0.014, 3&5: 0.032
Mild	-	-	6	100	4	66.7	1	16.7	1	16.7	
Moderate	2	33.3	-	-	-	-	1	16.7	2	33.3	
Severe	4	66.7	-	-	-	-	-	-	3	50	
Loss of surface epithelium											
None	-	-	6	100	5	83.3	4	66.7	1	16.7	1&2: 0.007, 1&3: 0.029, 2&5: 0.036,
Mild	3	50	-	-	1	16.7	2	33.3	1	16.7	
Moderate	1	16.7	-	-	-	-	-	-	2	33.3	
Severe	2	33.3	-	-	-	-	-	-	2	33.3	
Fibrosis/fibroblast increase											
None	-	-	6	100	5	83.3	6	100	-	-	1&2: 0.007, 1&4: 0.07, 2&5: 0.007, 3&5: 0.025, 4&5: 0.007
Mild	1	16.7	-	-	1	16.7	-	-	2	33.3	
Moderate	4	66.7	-	-	-	-	-	-	3	50	
Severe	1	16.7	-	-	-	-	-	-	1	16.7	

**Table 2** (continued)

Distribution of histopathological findings according to groups	1. Group	2. Group	3. Group	4. Group	5. Group	P
Mucosal thickness						
< 200 µm	–	5	83.3	4	66.7	–
201–250 µm	1	16.7	1	16.7	2	33.3
251–300 µm	2	33.3	–	–	–	–
> 300 µm	3	50	–	–	–	–
Epithelial thickness						
One cell	–	6	100	5	83.3	–
Two cells	2	33.3	–	–	–	–
Three cells	1	16.7	–	1	16.7	5
Four and over cells	3	50	–	–	–	1
Increase in mucous gland						
None	4	66.7	5	83.3	4	66.7
Mild	–	1	16.7	2	33.3	2
Moderate	1	16.7	–	–	–	–
Severe	1	16.7	–	–	–	–
Papillary projections						
None	–	2	33.3	2	33.3	4
Mild	2	33.3	2	33.3	3	50
Moderate	1	16.7	2	33.3	1	16.7
Severe	3	50	–	–	–	–

## Edema

Edema in the subepithelial area was recovered in groups 3 and 4 in comparison with groups 1 and 5 with statistical significance. In this parameter, xylitol showed better improvement than mometasone numerically (Fig. 2b, c).

## Loss of cilia and epithelium

Loss of cilia structures on pseudo stratified columnar epithelium and disruption of epithelium itself recovered in groups 3 and 4, nearly the same values and that's statistically significant. In the parameter of loss of surface epithelium, not a significant statistical value was obtained between groups 3 and 5, and between 4 and 5 (Fig. 2d, e).

## Squamous metaplasia

It refers to the transformation of the ciliated columnar epithelium to the stratified squamous epithelium. It is a protective, resistant but non-functional tissue. The evident improvement was achieved in groups 3 and 4, and statistical significance was obtained between groups 3 and 5, and between groups 4 and 5. This result may be due to that squamous metaplasia was mostly seen in group 5. It can be explained that the result may also be due to squamous metaplasia which is a protective tissue forms ciliated columnar epithelium later (Fig. 3a).

## Chronic inflammatory cell infiltration and fibrosis

Densely lymphocytic infiltration was seen and in some areas fibrosis and an increase in the number of fibroblasts were seen too. Groups 3 and 4 showed a statistically significant recovery. In these parameters, mometasone is found more effective than xylitol. This can be explained as the anti-inflammatory potential of nasal steroid (Fig. 3b, c).

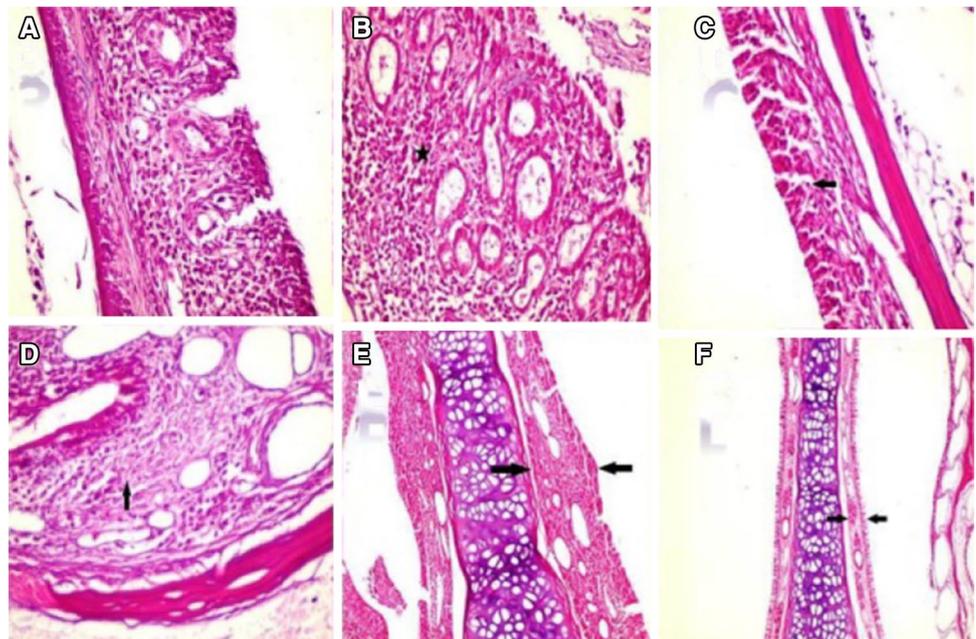
## Mucosa and epithelium thickness

The increase in the thickness of the mucosa is caused by edema, congestion, and chronic inflammatory cell infiltration (Fig. 3d, e). The increase in the thickness of the epithelium is caused by stratification of epithelial cells (Fig. 4a, b). The thickness of the mucosa and epithelium is decreased in groups 3 and 4, nearly normal values in group 2. Statistically significant value was obtained.

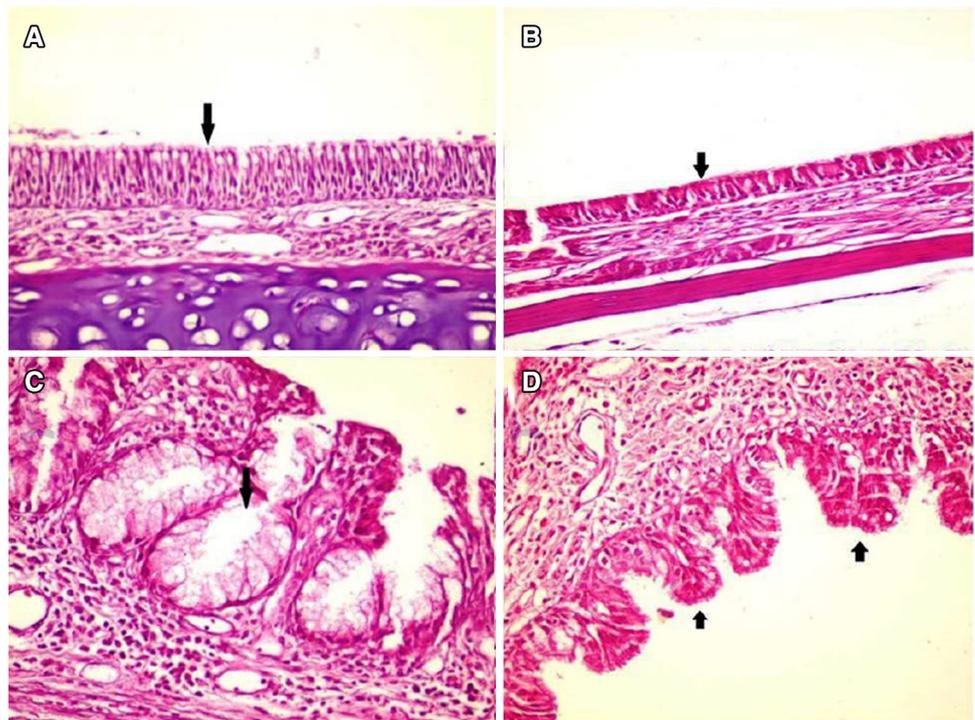
## Mucous glands

Increased number of mucous glands is a metaplastic condition that occurs in the chronic inflammatory process. In group 1, it is seen in 33% but in group 5, it is seen in all animals with different degrees. So, analysis between groups 3 and 5, and between groups 4 and 5 gave the result of improvement with statistical significance. Xylitol and mometasone showed the same effect (Fig. 4c, d).

**Fig. 3** **a** Squamous metaplasia on the left side in the patient group (group 1), columnar epithelium on the right (H&E  $\times$  400). **b** Intensive chronic inflammatory cell infiltration in the patient group (Group 1) (H&E  $\times$  400). **c** Minimal chronic inflammatory cell infiltration in the xylitol group (3rd group) (H&E  $\times$  100). **d** In the control group (group 5), fibroblast growth in the lamina propria and the presence of collagen (H&E  $\times$  400). **e** Thickened mucosa in the patient group (group 1) (Over 300  $\mu$ m) (H&E  $\times$  100), **f** fine mucosa in the xylitol group (3rd group) (H&E  $\times$  100)



**Fig. 4** **a** Four to five cells arranged within epithelium in the treatment control group (group 5) (H&E  $\times$  400). **b** One to two cells arranged within epithelium in group 3 (H&E  $\times$  400). **c** Increased mucus gland in the treatment control group (5th group) (H&E  $\times$  400). **d** Papillary projections in the treatment control group (5th group) (H&E  $\times$  400)



## Discussion

Rhinitis medicamentosa is a disease that occurs by abuse of topical decongestants. Its clinical manifestation is mainly nasal obstruction due to congestion [2, 3]. But beyond that, it is a mucosa and submucosa disease with its few histopathologic signs [5, 6]. It is hard to manage this disease. Ceasing of topical decongestants is the first choice of therapy. But, rebound congestion makes patients inevitable. Topical nasal steroids are known and mostly prescribed, effective drugs [4]. It has anti-inflammatory and anti-edema effect. Currently, there is no detailed study of nasal steroids in the treatment of rhinitis medicamentosa. But there are animal studies that show us that nasal steroids can be used for treatment. So those are mostly prescribed medications for rhinitis medicamentosa. Saline solutions can be also used to moisture nasal mucosa. Systemic steroid therapy may be helpful, but no evidence-based data exist. Antihistaminics may help patients who have allergic symptoms [3].

Taş et al. performed a study with 24 guinea pigs in a similar experimental setting of the present study [14]. In this study, the effectivity of mometasone was researched in rhinitis medicamentosa. The study does not have detailed statistical analysis but has given important histopathologic information. It has noted that mometasone nasal spray was effective against experimentally induced rhinitis medicamentosa. Another study that performed on guinea pigs 2 months long oxymetazoline induced to rhinitis medicamentosa and histopathologic study has revealed edema in

epithelial and subepithelial tissue [15]. In this study, marked congestion was also noted. 14 days of fluticasone therapy decrease the edema and congestion and no sign of tissue disruption. Vaidyanathan et al. performed a human study where subjects received oxymetazoline for 14 days and developed rebound congestion, treated by fluticasone, and so the results were obtained by rhinomanometry [17]. The result showed that fluticasone removed the tachyphylaxis effect that was induced by oxymetazoline.

Recently, there have been some publications related to various treatment options such as endonasal UV phototherapy, topical hyaluronic acid, and anti-mucolytic erdosteine in the treatment of rhinitis medicamentosa [18–20]. Nevertheless, in literature, except nasal steroids and some others as abovementioned, there are no other drugs used in studies about rhinitis medicamentosa. As a hypothesis, the xylitol solution can be thought in the treatment of rhinitis medicamentosa. Xylitol is a sugar structured material that has properties especially hydrophilicity [8, 13]. It is an osmoregulator substance, so balances the water content of the nasal mucosa. It has also an antibacterial effect that some organisms cannot metabolize xylitol as glucose [10–12]. On account of this property, xylitol has been famous to decrease dental caries.

Nasal irrigation solution including Xylitol is in the the market in several countries. This study was not performed by a solution in the market. Xylitol solution was prepared from crystal form and dissolved in the saline up to concentration 5%.

In the present study, xylitol is compared with mometasone, a known effective drug [14]. Xylitol is found that as effective as mometasone to heal the histopathologic parameters, such as congestion, edema, cilia, epithelial loss, squamous metaplasia, and mucous gland increase. Chronic inflammatory cell infiltration and fibrosis answered to mometasone better than xylitol as expected, because of its steroid structure that has a potent anti-inflammatory effect.

The results of this study reveal that xylitol is an effective drug as nasal steroids in the treatment of rhinitis medicamentosa. It has a mucosa healing effect by its molecular properties. It is cheap and has no side effects. Beyond this study, studies with electron microscopic data in larger samples must be achieved, and human studies with rhinometric values are required.

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